REMARKS

I. Amendments to the Claims

Claim 6 has been amended to incorporate the method steps of claim 11. Claim 42 has been amended to delete dependency on claim 11.

Claim 11 has accordingly been cancelled.

No new matter has been added.

II. Claim Objections

The Examiner objects to a typographical error in claim 11. Claim 11 has been cancelled, thereby obviating the objection. Applicants request that the objection be withdrawn.

III. Claim Rejections - 35 USC § 112

Applicants have amended claim 6, thereby obviating the Examiner's rejection. Applicants request that the rejection be withdrawn.

IV. Claim Rejections - 35 USC § 103

The Examiner rejects 6, 11, 14, 18, and 41-47 under 35 U.S.C. 103(a) as being unpatentable over Azuma (EP 1097715 Al, cited in prior action) in view of Van Nest et al. (EP 0399843 A2). The Examiner indicates that despite Applicants' arguments establishing that Van Nest is directed to "the preparation of a different composition than the instantly claimed composition," one of skill in the art would have a reasonable expectation of success because both Azuma and Van Nest are "directed to the production of oil in water emulsions comprising bacterial cell walls." (Office Action, page 7, bottom paragraph). Applicants submit that the Examiner has misconstrued the arguments presented in the Amendment dated December 10, 2007.

The Examiner states that Applicants essentially suggest that Van Nest teaches a "different" composition from the invention because the "applicant's compositions comprise more

cell wall components than those of Van Nest." However, Applicants emphasize that using BCG-CWS according to Van Nest would not work to obtain a cell wall paste having the claimed particle-size distribution. The muramyl peptides are a low molecular weight compound and merely one unit of the peptideglycan that is part of BCG-CWS. Because of the large molecular weight of the components and complicated structures of the BCG-CWS composition, the physical properties of BCG-CWS are different from the cell wall preparations of Van Nest. That is, the solubility is significantly different.

Consequently, Applicants submit that the disclosure of Van Nest in combination with Azuma is not enabling for the present invention. If one of skill practices the prior art using BCG-CWS, the poorly-soluble macromolecule particles would aggregate and adhere to the wall of the container. (See Declaration, page 3). However, the lower molecular weight particles such as muramyl peptide could be formulated as an emulsion or a lyophilized composition far more easily without problems. This assertion is supported by the fact that Van Nest does not provide a working example using killed mycobacterium. (See Declaration, page 3). Therefore, one of skill would not look to the method of Van Nest to provide a smaller particle.

Furthermore, Van Nest emphasizes that the process by which the molecules are emulsified is important to the ultimate particle size. (See Van Nest page 7, lines 15-21). However, Azuma does not disclose the specific emulsifying steps recited in the instant claims. By preparing the oil-in-water emulsion according to the steps recited in claim 6, i.e., mixing BCG-CWS and squalane in hexane or heptane comprising 5-20% (v/v) of ethanol to disperse the cell wall components, and then removing the solvent by distillation, the resulting emulsion achieves a very uniform particle dispersion. In contrast, using heptane or toluene alone does not achieve the uniform particle dispersion. (See Specification, Example 10, Table 12, and Declaration page 5).

Therefore, the passage the Examiner relies on to provide a method for decreasing droplet size (Van Nest page 12, lines 21-25) does NOT describe or suggest an operative method to

reduce droplet size of emulsions comprising BCG-CWS. Similarly, Azuma does not teach the claimed particle size using non-polar solvents, especially the hexane or heptane/ethanol solution. Azuma also does not suggest any way to reduce the droplet size of emulsions of the large molecular-weight composition of the presently claimed cell paste.

Thus, one of skill would not have been able to make the present invention from the combined disclosures of Van Nest and Azuma.

Unexpected Results of the Present Invention

Applicants further submit that even if a *prima facie* case of obviousness has been shown by the Examiner, the unexpected beneficial properties of the present invention overcome any such *prima facie* case of obviousness. The Declaration of Dr. Nomura explains that the physical properties of the present invention when prepared using the method disclosed in claim 6 lead to an unexpected particle size distribution (Declaration, page 4-5), and that the particle size distribution obtained leads to improved emulsification and improved stability after resuspension. (Declaration, page 6).

The Examiner has failed to address the unexpected result obtained by use of the combined heptane/ethanol solvent to prepare the formulation of the invention explained beginning at the bottom of page 9 of the Applicants' prior Amendment. This is relevant as distinct properties of the formulation result.

Applicants submit that any assertion of obviousness has been overcome by the unexpected physical properties of the present invention. Applicants request that the rejection be withdrawn.

CONCLUSION

In view of the above remarks, Applicants submit that claims are allowable. The favorable actions of withdrawal of the standing rejections and allowance of the claims are requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell Reg. No. 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: November 7, 2008

Respectfully submitted,

By _____
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Attachment: Declaration of Dr. Nomura